UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/639,207	08/14/2000	Parsa Kazemi-Esfarjani	06618-686001	9459

20985 7590 10/02/2002

FISH & RICHARDSON, PC
4350 LA JOLLA VILLAGE DRIVE
SUITE 500
SAN DIEGO, CA 92122

EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	9

DATE MAILED: 10/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/639,207	Applicant(s) KAZEMI-ESFARJANI ET AL.	
	Examiner Daniel Sullivan	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7,9-26 and 28-79* is/are pending in the application.

4a) Of the above claim(s) *47-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-,35-7,9-26,28-46 and 50-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a Non-Final response to the Amendment and Response to the First Action on the Merits filed July 2, 2002 (paper #8). Claims 4, 8 and 27 were cancelled in paper #8. Claims 1, 2, 5, 6, 9-13, 25, 26, 28-46 and 50, amended in paper #8, and claims 3, 7 and 14-24, as originally filed, are pending in the application.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the Declaration is not legible. Applicant, in response to the Office Action (paper #7), has agreed to provide a new Declaration.

Specification

Objection to the specification because of missing text is withdrawn in view of the amendments to the specification filed in paper #8.

Claim Objections

Claim 50 is objected to because of the following informalities: the claim contains markings to show changes made in step (b). Applicant must provide a clean copy of the amended claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-7, 9-26, 28-46 and 50 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for genes that modulate polyglutamine toxicity comprising: providing a *D. melanogaster* expressing a polyglutamine sequence, wherein the sequence produces polyglutamine toxicity in *D. melanogaster*, and breeding the first *D. melanogaster* to a second *D. melanogaster*, wherein the second *D. melanogaster* has P transposable element inserted into its germline, thereby producing progeny, and screening the progeny for increased or decreased polyglutamine toxicity relative to the first *D. melanogaster*, and identifying one or more genes adjacent to or having an insertion of the P element sequence that confers increased or decreased polyglutamine toxicity, does not reasonably provide enablement for a method of screening for genes that modulate polyglutamine toxicity in any and all species of *Drosophila* or for any and all transposable elements in *D. melanogaster*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicant's arguments have been fully considered but are not found to be persuasive. In response to the First Office Action, Applicant argues that the disclosure is enabling for all species of *Drosophila* because "the P transposable element is not limited to the *melanogaster* species of the genus *Drosophila*" (paper #8, page 10, last line of the first full paragraph). The argument is not persuasive because making and using the claimed invention requires more than

the presence of a P element. The genetic analysis of the claimed invention requires that the transposable element used be highly mobile within the experimental animal so that a useful library of mutants can be generated. A transposable element that produced mutations at a low frequency would not be useful because screening would be prohibitively slow. The unpredictability of practicing the invention in any and all species of *Drosophila* is illustrated in the teaching of Atkinson and O'Brochta (*Ann. Ent. Soc. Am.* (1999) 92: 930-936), "excision frequency of P was found to decrease in drosophilid species distantly related to *D. melanogaster*" (final sentence on page 930). The teachings of the prior art and specification do not provide a means to distinguish species of *Drosophila* that can be used to practice the invention from species that would not work or a means to increase excision frequency in species of *Drosophila* that are distantly related to *melanogaster* without empirical experimentation. Therefore the teachings of the specification and prior art would not allow one of ordinary skill to practice the invention in any and all species of *Drosophila* without an undue burden of empirical experimentation.

Applicants argue that the claims are enabled for the use of transposable elements other than the P transposable element because, "as many as 30 classes of transposons have been found in *Drosophila*" (final sentence of page 10), and provides the "copia" class of transposable element as an example of another transposon that has been used in classical *Drosophila* genetics. Applicant then asserts that, "[s]uch transposable elements provide the means to develop vectors that modulate expression of a given gene in a particular tissue through fusion of the gene to a specific promoter" (page 11, first paragraph). However, although the art teaches many transposable elements in *Drosophila* only a minority of these have ever been used as vectors. For

example, Atkinson and O'Brochta teach, "transposable element work focused mainly on the class II elements...because although several class I retrotransposable elements had been identified and characterized from *D. melanogaster*, none had been used as a transformation vector" (page 931, second full paragraph). While it is true that the existence of alternative transposable elements provide a means to develop vectors that can be used according to the present invention, neither the art nor the teachings of the specification provide guidance that would allow one of ordinary skill to make such vectors without undue experimentation.

Claim 50 stands rejected under 35 U.S.C. §112, first paragraph because the specification does not disclose how to detect polyglutamine toxicity in a single cell. Applicant did not respond to the examiner's argument.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Rejection of claims 5, 6 and 9 is withdrawn, as the claims have been amended such that the claims are no longer indefinite. Rejection of claims 21 and 33 is withdrawn in view of Applicant's clarification (paper #8, page 12, fourth full paragraph). Rejection of claim 50 as being indefinite for failing to recite a fertilization step and implantation step is withdrawn. The claim, as amended, is no longer indefinite. Rejection of claim 50 for recitation of "a length sufficient to produce polyglutamine toxicity", is withdrawn in view of applicants clarification (paper #8, beginning page 12, final paragraph through the first paragraph of page 13).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26, 28, 32-34, 37, 39-41 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Warrick et al. (1998) *Cell* 93:939-949 as evidenced by Paulson (1997) *Neuron* 19:333-344.

Claims 26, 28, 32-34, 37 and 39-41 are drawn to a transgenic *Drosophila* comprising a transgene containing a plurality of CAG's and at least one CAA sequence encoding a polyglutamine repeat sequence. Claim 28 limits the *Drosophila* to *Drosophila melanogaster*; claim 32 limits the ratio of CAG's to CAA's encoding the polyglutamine repeat sequence to about 10:1 to 50:1; claim 33 limits the control element for expression of the polyglutamine sequence to a constitutive, regulatable or tissue specific control element; claim 34 limits the tissue specific control element of claim 33 to a control element that confers neural, retinal, muscle or mesoderm cell expression. Claim 37 limits the polyglutamine sequence to between 50 and 100 amino acids in length; claim 39 limits the polyglutamine sequence to between about 50 and 200 amino acids in length; claim 40 limits the polyglutamine sequence to a sequence further comprising a tag; and claim 41 limits the *Drosophila* to a *Drosophila* wherein polyglutamine toxicity is produced in one or more tissue or organs of the animal. Claim 50 is drawn to a method of producing a transgenic *Drosophila* characterized by polyglutamine toxicity comprising: (a) transforming a *Drosophila* embryo or fertilized egg with a transgene comprising a plurality of

CAA and CAG sequences encoding a polyglutamine sequence having a length sufficient to produce polyglutamine toxicity in the *Drosophila*; and (b) selecting a *Drosophila* that exhibits polyglutamine toxicity in one or more tissues.

Warrick teaches a transgenic *Drosophila melanogaster* comprising a transgene containing a plurality of CAG's and at least one CAA wherein the CAG's and CAA's are present in a ratio of about 40:1 (two CAA resides in a total of 78 codons) and fused to a hemagglutinin epitope tag (see especially the description of the MJD construct on page 948 beginning the final sentence of column 1 and continuing through the first paragraph of column 2; also see the attached sequence file showing the codons comprised within the polyglutamine portion of the MJD1 coding sequence, this sequence was expanded to 78 glutamines by insertion of CAG repeats (see Paulson page 342, first paragraph of column 2). Warrick also teaches targeted expression of an expanded polyglutamine sequence wherein the promoter comprises an inducible promoter comprising a GAL4 responsive sequence, wherein tissue specific expression (i.e. neural, mesoderm, muscle and eye specific expression) is conferred through tissue specific expression of GAL4 (see especially the second column of Table 1 on page 940). Warrick also teaches a method of producing a transgenic *Drosophila* characterized by polyglutamine toxicity comprising generating transformant lines by "standard procedures" (final sentence of the first paragraph in the second column of page 948), which one of ordinary skill in the art would understand to comprise transforming a *Drosophila* embryo or fertilized egg with the transgene, and selecting a *Drosophila* that exhibits polyglutamine toxicity in one or more tissues (see especially Table 1 and the caption thereto).

The transgenic *Drosophila melanogaster*, transgene, polyglutamine sequence, control element and method of producing a transgenic *Drosophila* taught by Warrick are the same as those taught in the instant application, therefore the limitations of the claims are met by Warrick.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejection of claims 1, 4-16, 20-35, 41, 42 and 50 under 35 U.S.C. §103 is withdrawn in view of Applicant's cancellation of claims 4, 8 and 27 and amendment of claim 1 such that the claims are now drawn to a method of screening and mating progeny which comprise a *Drosophila* having a marker sequence inserted into its germline, wherein the marker sequence comprises 1) an inducible upstream activating sequence, 2) a minimal promoter sequence and 3) 5' and 3' transposable elements. Neither Warrick nor Tsubota, cited in the previous office action (paper #7), teach a marker sequence with these limitations.

Claims 1, 5-7, 9-14, 17-26 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Warrick et al. (*supra*) in view of Rørth (1996) *Proc. Natl. Acad. Sci. U.S.A.* 93:12418-12422.

The claims are drawn to a method of screening for genes that modulate polyglutamine toxicity comprising: (a) providing a first *Drosophila* expressing a polyglutamine sequence, wherein the sequence produces polyglutamine toxicity; (b) breeding the first *Drosophila* to a

second *Drosophila*, wherein the second *Drosophila* has a marker sequence inserted into its germline, wherein the marker sequence comprises 1) an inducible upstream activating sequence, 2) a minimal promoter sequence and 3) 5' and 3' transposable elements; (c) producing progeny from the breeding of the first *Drosophila* with the second *Drosophila*; d) screening the progeny for increased or decreased polyglutamine toxicity relative to the first *Drosophila*; and (e) identifying one or more genes operationally-associated with the marker sequence, or having an insertion of the marker sequence, that confers increased or decreased polyglutamine toxicity.

Warrick teaches a *Drosophila* expressing a polyglutamine sequence, wherein the sequence produces polyglutamine toxicity (see especially Table 1 and the caption thereto), breeding said *Drosophila* expressing a polyglutamine sequence with a second *Drosophila* comprising a second mutation (i.e. expression of the baculoviral antiapoptotic gene *P35*), and screening the progeny for increased or decreased polyglutamine toxicity relative to the first *Drosophila* (see especially page 945, beginning in column 1, **Blocking Apoptosis Mitigates Cell Degeneration Induced by Expanded Polyglutamine**, and Figure 6 and the caption thereto). Warrick also teaches that the *Drosophila* expressing a polyglutamine sequence can be used with, "*Drosophila* genetics to identify genes that can delay or prevent deleterious consequences of the polyglutamine-repeat proteins on neuronal integrity". Warrick does not teach a second *Drosophila* having a marker sequence inserted into its germline, wherein the marker sequence comprises 1) an inducible upstream activating sequence, 2) a minimal promoter sequence and 3) 5' and 3' transposable elements or identifying one or more genes operationally-associated with the marker sequence, or having an insertion of the marker sequence, that confers increased or decreased polyglutamine toxicity.

Rørth teaches a *Drosophila* having a marker sequence inserted into its germline, wherein the marker sequence comprises 1) an inducible upstream activating sequence, 2) a minimal promoter sequence and 3) 5' and 3' transposable elements and identifying genes operationally-associated with the marker sequence (see especially page 12421, column 2, first to third full paragraph). Rørth also teaches that, "[c]ontrolled overexpression can also identify important genetic interactions; if increased expression of one gene enhances or suppresses the phenotype of a mutation in another gene, their products are likely to be involved in the same process" (page 12418, column 1, final paragraph of column 1).

Thus, in combination, Warrick and Rørth teach all of the limitations of the broadest embodiment of the claimed invention. Further, they each teach that their methods can be combined with other methods for the purpose of identifying genes that interact with mutant genes (i.e. Warrick teaches using *Drosophila* genetics to identify genes that delay or prevent polyglutamine-repeat toxicity and Rørth teaches using controlled overexpression to identify gene interactions). Therefore the materials and teaching to combine the materials to produce the claimed invention were available to the skilled artisan prior to the effective filing date of the application. Thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Warrick and Rørth according to the teachings of the instant application. Motivation to combine these teachings comes from Warrick, who teaches that the fly model of polyglutamine toxicity can be used to identify additional genes that can mitigate neurodegeneration in humans (page 940, final sentence of the first full paragraph), and from Rørth who teaches that the methodology described provides "a novel genetic approach to link genes and function in higher eukaryotes: identifying genes that, when over- or

misexpressed...modulate an existing mutant phenotype" (page 12422, first full paragraph). A reasonable expectation of success is also provided by Warrick, who teaches, "[o]ur studies with *P35* indeed demonstrate that this system can effectively be used to define genes or factors that can mitigate degeneration" (page 948, second full paragraph) and Rørth who teaches, "target lines are easy to generate and...induced, mutated genes are easily identified" (page 12422, first full paragraph).

The limitations of more specific embodiments of the claimed invention are also taught by Warrick and Rørth. Claim 2 is directed to the method further comprising identifying a mammalian homologue of the gene of claim 1, and claim 3 limits the mammalian homologue of claim 2 to a human homologue. Warrick teaches that the described system can be used to identify genes that can mitigate neurodegeneration in humans (page 940, first full paragraph), which one of ordinary skill in the art would understand to comprise identifying the human homologue of the *Drosophila* gene.

Claim 5 limits the *Drosophila* to *Drosophila melanogaster*, which is taught by both Warrick and Rørth. Claim 6 limits the transposable element to a P transposable element; claim 7 limits the marker sequence to a sequence comprising a polynucleotide sequence that disrupts or alters expression of one or more genes near the sequence; claim 9 limits the inducible upstream activating sequence to a sequence that increases or decreases expression of one or more operationally-associated gene(s); claim 10 limits the second *Drosophila* to a *Drosophila* selected from a group of two or more animals having markers inserted into different locations of its genomic DNA; claim 11 limits the second *Drosophila* of claim 10 to a *Drosophila* selected from a group of 10-100, 100-500, or 500 or more animals; claim 12 limits the second *Drosophila* to a

Drosophila selected from a library of animals having markers inserted at random locations; and claim 13 limits the library of claim 12 to a library of *Drosophila* generated by random P element insertion. Rørth teaches a P transposable element that alters expression of one or more genes near the sequence comprising an inducible upstream activating sequence that increases expression of operationally-associated genes (see especially **Construction of Target Elements** in the second column of page 12418). Rørth also teaches a library of 163 target lines having markers inserted at different locations of its genomic DNA (see especially Figure 1(C) and the caption thereto) at random locations generated by P element insertion (see especially **Transformation and Fly Work** in the second column on page 12418).

Claim 14 limits the polyglutamine sequence to a sequence having between about 30-50 or about 50-100 glutamine residues. Claim 17 limits the polyglutamine sequence to a sequence comprising a tag; claim 18 limits the tag of claim 17 to an epitope tag; claim 19 limits the epitope tag to a tag comprising an hemagglutinin sequence; and claim 20 limits the nucleic acid encoding the polyglutamine sequence to a polynucleotide containing a plurality of CAG's, CAA's or a combination thereof. Warrick teaches a polyglutamine sequence having 78 residues encoded by a plurality of CAG's and CAA's and comprising a hemagglutinin epitope tag (see especially **MJD Constructs and Transformation** beginning in the first column of page 948 and continued in the second column of that page and citations therein).

Claim 21 further limits the method of claim 20 to a method wherein expression of the polynucleotide is conferred by a constitutive, regulatable or tissue specific expression control element; claim 22 limits the regulatable control element of claim 21 to an inducible or repressible element; claim 23 limits the regulatable element of claim 21 to an element

comprising a GAL4 responsive sequence; and claim 24 limits the tissue specific element of claim 21 to an element that confers neural, retinal, muscle or mesoderm cell expression. Warrick teaches targeted expression of an expanded polyglutamine sequence wherein the promoter comprises an inducible promoter comprising a GAL4 responsive sequence, wherein tissue specific expression (i.e. neural, mesoderm, muscle and eye specific expression) is conferred through tissue specific expression of GAL4 (see especially the second column of Table 1 on page 940).

Claim 25 is drawn to a progeny *Drosophila* produced by the method of claim 1. The limitations of claim 26, as well as the teachings of Warrick regarding claim 26 are recited above. Claim 42 is drawn to the a transgenic *Drosophila* of claim 26, further comprising a marker sequence inserted into its genomic DNA wherein the marker is located adjacent to a gene or inserted into a gene whose expression or activity increases or decreases polyglutamine toxicity in the animal, and wherein the marker sequence comprises an inducible upstream activating sequence, a minimal promoter sequence and 5' and 3' transposon elements containing terminal inverted repeats. As described above, the combined teachings of Warrick and Rørth comprise all of the limitations of the *Drosophila* of claims 25, 26 and 42. Warrick and Rørth also provide direction and motivation to breed the *Drosophila* according to the method of the instant invention. Therefore the claimed progeny *Drosophila* would have been obvious to one of ordinary skill in the art at the time the invention was made.

Because Warrick and Rørth teach all of the limitations of the claims and, as described above, provide both direction and motivation to combine their independent teachings according

to the teachings of the instant application, each of the claims would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Anne-marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER

dms
September 24, 2002